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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/814,293	STARK ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

The Examiner thanks the Applicants for their timely reply filed on 21 December 2007, in the matter of 10/814,293. A response to the remarks and amendments are herein presented under 37 CFR § 1.113.

Response to Remarks/Arguments

The nonstatutory obviousness-type double patenting rejection made to Applicants' original claims 1-8 and 10-25 are hereby **withdrawn**, in view of the terminal disclaimer filed on 21 December 2007, and in compliance with MPEP 804.02(II) and 37 CFR 3.73(b).

The 35 USC §102(b) rejections made over Fulberth et al. (U.S. Patent 3,835,221) have been reconsidered in view of the arguments made by Applicants with regards to claims 1 and 9 and are hereby **withdrawn**.

The 35 USC §103(a) rejections made over Stark et al. (U.S. Patent 6,733,789) in view of Fulberth et al. (U.S. Patent 3,835,221) have been reconsidered in view of the arguments made by Applicants with regards to claims 1, 2, 5, 6 and 9, and are hereby **withdrawn**.

Claim Objections

Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The website (http://pharmacycode.com) teaches that the

hemifumarate and fumarate have the same formula, structures and properties. Since the compounds are the same, claim does not further limit claim 3.

Claims 6 and 22 objected to because of the following informalities: typographical errors. Appropriate correction is required.

Claim 6, as presently written, is missing the beginning of the sentence. Per the previously amended claim set filed 1 April 2004, claim 6 is written as being "A multiparticulate..." For the purposes of examination, the claim will be interpreted in light of its previous presentation. Appropriate correction is required.

Claim 22, as presently written, is dependent upon itself. Per the previously amended claim set filed 1 April 2004, claim 22 is written as being "presently amended" to be dependent from claim 1. The most recently amended set of claims, submitted 21 December 2007, recites the discrepant claim 22 as "previously presented". Therefore, the Examiner views the discrepancy as a typographical error only and will herein examine claim 22, as before, as being dependent from claim 1. Appropriate correction is required.

New Grounds of Rejection

Applicants have added new claims 26-32. Claims 1-32 now represent all claims currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. As amended, the instant claim set recites limitations to the claimed multiparticulate formulation such that the bisoprolol, bisoprolol salt and bisoprolol hemifumarate compounds are "enriched in the (S)-enantiomer" or are in the form of "enriched (S)-bisoprolol". After carefully examining the instant disclosure, the examiner respectfully submits that support for this amendment is lacking and the addition of said limitations is new matter. Specifically, the limitations referring to bisoprolol compounds "enriched in the (S)-enantiomer" or forms of "enriched (S)-bisoprolol" are not set forth in the instant specification. The instant specification, including the recited paragraph [0014] from US-PGPub 2004/0185099 (pg. 5, lines 20-24), has been carefully reviewed and sufficient support for the limitations to bisoprolol compounds "enriched in the (S)-enantiomer" or forms of "enriched (S)-bisoprolol" were not found.

It should be noted that in light of the above rejection, claims 26-32 will still be further examined on the merits, but absent the (S)-enantiomer limitation to bisoprolol.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It should be noted that the instant claims are product claims and any intended use recitation such as "being effective to achieve" in claim 1 and "effective to prevent" in claim 2, does not alone show patentable distinction. A recitation of intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. In other words, if the prior art structure is capable of performing the intended use then it meets the claim.

As to the recitation "at least" in claims 1 and 2 immediately preceding their respective time ranges (e.g. 4-6 hours) during which an initial lag of bisoprolol release is to be maintained. Despite the presence of the ranges, the limitation in each claim is interpreted as open-ended because the phrase "at least" is interpreted to have no upper limit and therefore allows the claims to read on embodiments outside the respective ranges.

The remaining claims are rejected since they depend from claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noda et al. (U.S. Patent 5,137,733) in view of Oshlack et al. (U.S. Patent 5,580,578).

The instant claims 1, 2, 26, 27 and 30 are drawn to a multiparticulate bisoprolol formulation wherein each particle comprises a core of bisoprolol or a pharmaceutically acceptable bisoprolol salt surrounded by a release-controlling, polymeric coating. Claims 3 and 28 further limit the drug to a pharmaceutically acceptable salt of bisoprolol (e.g. bisoprolol fumarate or hemifumarate). Dependent claims 4 and 29 further limit the bisoprolol salt of claim 3 to bisoprolol hemifumarate. Claims 5 and 6 recite *in vitro* release profile limitations to the formulation. Claims 7 and 8 further limit the composition of claim 1 such that a sealant is applied to the medicated core prior to application of the polymeric coating. Claim 9 further limits the formulation such that the bisoprolol active ingredient is applied to a core particle (e.g. non-pareil seed) having an average diameter between 400 and 1100 microns. Claims 10 and 11 further limit the polymeric coating of claim 1 wherein the polymer of claim 10 is a major proportion of the coating with low permeability and claim 11 is a minor proportion of the coating with high permeability. Claim 12 further limits the coating of claim 10 such the at least one of polymers is a methacrylic acid copolymer. Claim 13 further limits the coating of claim 10 such

the at least one of polymers is a ammonio methacrylate copolymer. Claim 14 further limits the polymer coating of claim 12 such that a mixture of polymers is used. Dependent claim 15 further limits the polymer coating by including one or more soluble excipients. The soluble excipients are further limited by category in (e.g. soluble polymer, surfactant, etc.) in claim 16 and by compound (e.g. PVP, PEG, and mannitol) in claim 17. Claim 18 further limits the soluble excipient of claim 15 such that the excipient is present between 1-10% by weight based on the total dry weight of the polymer. Claim 19 recites the addition of one or more auxiliary agents to the polymer coating. Claims 20 and 21 further limit the formulation of claim 1, such that the polymer coating contributes to the overall formulation, a given weight percentage of the core. Claim 20 recites a 10-100% weight gain on the core whereas claim 21 recites a 25-70% contribution. Claim 22 further limits the formulation of claim 1 (see Claim Objections above), such that a sealant is applied to the polymeric coating. Claim 23 recites useable examples for said sealant. Claim 24 recites different oral dosage forms that may encompass the bisoprolol formulation. Claim 25 further limits the type of tablet form of the formulation (e.g. disintegrating, effervescent, etc.). Claims 31 and 32 further limit the composition of claim 26 to particular amounts of bisoprolol.

Noda teaches a controlled release pharmaceutical preparation comprising a core containing a medicinal compound and a coating layer containing a water-repellant salt and a water-insoluble and slightly water-permeable acrylic polymer having a methacrylic copolymer group (claim 1). Example 12 teaches the medicinal agent to be bisoprolol fumarate. Noda also teaches that the system is designed to have an initial lag period before the medicinal agent is released or dissolved and that this initial period can be varied depending upon the number of

coating layers applied to the cores (col. 5, lines 19-56). Further, the preparation can retain an effective blood concentration for many hours and can again differ with the amount of layers applied to the cores (col. 5, lines 19-56). The preparation is suitable for a once-a-day administration (col. 6, lines 1-2). The website: http://pharmacycodc.com teaches that the hemifumarate salt and fumarate salt have the same formula and structures. Non-pareil seeds (e.g. spherical particles) are taught to have a mean diameter between 500 and 1000 microns (col. 3, lines 16-18). Fillers, as defined by applicant (pg. 14, lines 13-14), include magnesium stearate and calcium stearate, both of which Noda teaches in claim 1 as being part of the coating. An additional coating layer is added to the cores after the acrylic polymer layer (col. 2, lines 32-39). The acrylic polymers are taught at col. 2, lines 40-59 and include Eudragit RS as well as a combination of Eudragit RS and RL. Example 6 teaches a coating layer with the Eudragit RS/RL combination The additional coating layer is chosen from compounds such as hydroxypropyl cellulose (col. 2, lines 60-66). The amount of coating layer is about 5% to about 80% based on the weight of the core (col. 3, lines 11-21). Various excipients such as polyvinylpyrrolidone and mannitol are present in the core (col. 3, lines 37-57). The acrylic coating layer is further taught to comprise plasticizers (col. 4, lines 43-55). Still further, Noda teaches formulations with differing number of coating layers wherein the lag time and complete dissolution are different. Preparation (b) of Figure 1, prepared as polymer coated granular tablets in Test Example 1, exemplifies the dissolution profile of the instant claims.

While Noda teaches many of the limitations of the instant claims, the exact composition of the instant claims is not exemplified in the reference. That which is not expressly taught by Noda includes: application of the sealant is to the core prior to the application of the polymeric

coating, the percent soluble excipient used (e.g. 1-10%), the percent weight contributions to the overall composition by the polymeric coating, and the amount of bisoprolol added to the composition.

Oshlack et al. teaches a controlled release formulation wherein a barrier layer is incorporated between the medicinal core and the acrylic coating layer (col. 13, line 62 to col. 14, line 2). The barrier layer can be hydroxypropyl methylcellulose or any film-forming agent known in the art (col. 13, line 62 to col. 14, line 2). Eudragit RS/RL dispersions mixed together in the desired ratios are taught as the polymer coatings (col. 9, lines 47-54).

In view of the combined teachings of the prior art, one of ordinary skill in the art would have been motivated to prepare a controlled release system comprising bisoprolol fumarate in a core coated first, by a barrier layer and second by an acrylic polymer with a reasonable expectation of successfully obtaining the desired dissolution pattern of the drug from the dosage. Oshlack et al. teach that it may be desirable to obtain the desired efficacy by utilizing different coating components to effect an overall release of the active agent within the desired levels over a longer period of time (col. 18, lines 3-11). Therefore, modification of the instant dosage formulation to apply the barrier layer (e.g. hydroxypropyl methylcellulose) prior to applying the polymeric coating, as earlier defined, is well within the purview of the skilled artisan.

Furthermore, it is *prima facie* obvious to switch the order of addition of said barrier and polymeric layer(s) to the formulation with the result being that of the controlled release composition of Applicant's instant claims 1-32. The basis for this *prima facie* obviousness rejection can be found in the following case law: *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946), wherein selection of any order of performing process steps is prima facie obvious

in the absence of new or unexpected results; and *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930), wherein selection of any order of mixing ingredients is *prima facie* obvious.

Neither reference teaches the percentage of soluble excipient included in the polymeric coating (e.g. 1-10%), the percent weight gain of the formulation contributed by the polymeric coating (e.g. 10-100% and 25-70%) or the amount of bisoprolol added to the formulation (claims 31 and 32) as claimed by the Applicants. Since the value of each parameter with respect to the claimed dosage form is adjustable, it follows that each is a result-effective parameter that a person having ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of bisoprolol to add to the dosage formulation as well as the optimal percentages of coating and excipient to include in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these ingredient amounts would have been obvious at the time of Applicant's invention.

No claims are allowed.

Conclusion

Due to the new grounds of rejection, this action is deemed **non-final**.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/Michael P Woodward/
Supervisory Patent Examiner, Art Unit 1615